REMARKS/ARGUMENTS

In response to the Office Action of July 13, 2005, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claims 1, 39, 40 and 44 have been amended. Claims 2-38 were cancelled in a previous response (filed on December 10, 2004). Claims 39-46 are withdrawn from consideration. It is understood that claims 39-46, drawn to the non-elected invention, will remain pending, albeit withdrawn from prosecution on the merits at this time. If the examined claim of the Group I invention is deemed to be allowable, rejoinder of the remaining claims (39-46) in accordance with the decision in *In re Ochiai* is respectfully requested; since the remaining claims (39-46) are limited to the use of the biopolymer marker of claim 1 (the examined claim of the elected Group I invention).

Claim 1 is under examination. Claims 1 and 39-46 remain pending in the instant application.

No new matter has been added by the amendments to the claims made herein.

Claim 1 has been amended to clearly indicate that the biopolymer marker consisting of SEQ ID NO:3 evidences a link to

Alzheimer's disease. This amendment is supported by the specification as originally filed; page 35, lines 14-18, disclose that an objective of the invention is to evaluate samples containing a plurality of biopolymers for the presence of disease specific biopolymer markers which evidence a link to at least one specific disease state and page 46, line 15, to page 47, line 10 identifies SEQ ID NO:3 as a biopolymer related to the specific disease, Alzheimer's disease.

Claims 39 and 44 have been amended to remove the term "isolated".

Claim 40 has been amended to provide proper antecedent basis to the term "sample" in parent claim 39.

Request for Rejoining of Claims

Considering that claims 39-46 are limited to the use of SEQ ID NO:3 a search of these claims would encompass this specific sequence. The instant application is related in claim format to several other applications, both pending and issued, of which serial number 09/846,352 is exemplary. In an effort to maintain equivalent scope in all of these applications, Applicants respectfully request that the Examiner consider rejoining claims 39-46 in the instant application, which are currently drawn to non-elected Groups, with claim 1 of the elected Group under the

decision in *In re Ochiai* (MPEP 2116.01), upon the Examiner's determination that claim 1 of the elected invention is allowable and in light of the overlapping search. If the biopolymer marker of SEQ ID NO:3 is found to be novel, methods and kits limited to its use should also be found novel.

Rejection under 35 USC 101

Claim 1, as presented on March 31, 2005, remains rejected under 35 USC 101 because the claimed invention allegedly has no apparent or disclosed specific and substantial credible utility.

The Examiner asserts that the disclosure does not clearly correlate sequences consisting of SEQ ID NO:3 with a link to Alzheimer's disease. Specifically, the Examiner asserts that although the instant specification discloses that SEQ ID NO:3 is related to Alzheimer's disease, the asserted specific utility is not credible because Figures 1, 3 and 6 do not exemplify SEQ ID NO:3 as measurable in patients with Alzheimer's disease or undetectable and regulated differently in normal patients.

The Examiner appears to believe that the instant invention discloses a marker (claimed SEQ ID NO:3) that is found in Alzheimer's disease patients and not found in normal patients.

Applicants respectfully submit that the Examiner is incorrect.

The claimed biopolymer marker (SEQ ID NO:3) is found in

patients age-matched with the Alzheimer's patients and not found in Alzheimer's patients. This phenomenon can be observed in the figures as originally filed and is explained at various points in the previous response filed on March 31, 2005 (see, for example, page 28 and 34). Additionally, the instant specification as originally filed clearly indicates that the criteria for labeling a peptide a "marker" is differential expression in disease vs. normal, i.e. the definition of "marker" according to the invention is not limited to peptides found in a disease state and absent in a normal state (for example, see page 5, lines 12-20). Considering that, in the instant application, the claimed marker (SEQ ID NO:3) is found in patients age-matched to Alzheimer's patients, it is in accordance with the invention that the figures do not exemplify SEQ ID NO:3 as measurable in Alzheimer's disease patients.

The Examiner asserts that Band 4 is identified in Figure 1 as containing the CENP-E protein and 3 unknown proteins; therefore the appearance of Band 4 may be attributed to either of the four proteins therein and it is not clear how Band 4 is unique to only sequences consisting of SEQ ID NO:3.

According to the method of the invention, the criteria for evaluation is specific ions which can be identified from the band on the gel and not the appearance of the band itself; i.e. peptides are selected for identification based on differential expression

observed in gels but are ultimately identified by mass spectrometry not by gel electrophoresis. A hypothetical example may serve to clarify. For example, a researcher has found that Band X is differentially expressed between a lung cancer patient and a patient who was determined to be healthy with regard to lung cancer. In hope of identifying potential markers for lung cancer, the researcher subjects Band X to mass spectrometry and obtains three distinct mass spectral profiles. Two of these mass spectral profiles match to known proteins, Protein A and Protein B which the researcher then identifies as potential markers for lung cancer. The fact that multiple peptides were identified from one band does not diminish the value of the peptides as markers since it is the mass spectral profile which is unique and not the band. If a peptide is identified in a particular band, then it is present in the band regardless of the presence and/or absence of other peptides/proteins within the same band.

The Examiner makes several assertions regarding the figures presented in the instant application.

In response to the Examiner's assertions, Applicants herein provide the attached Declaration (and figures) under 37 CFR 1.132. The figures attached to the declaration were produced by scanning the original photographs of the gels. No new matter has been added; these figures are simply clearer copies of Figures 1, 3 and 6 as

originally filed and are provided to clarify the differential expression of Band 4. The figure entitled "DEAE 5(E) Ad vs. Age Matched AD" represents Figure 1. The figure entitled "DEAE 6(Elution) AD vs. Age Matched AD (Control)" represents Figure 3. The figure entitled "HiS 1 (scrub) AD vs. Age Matched AD (Control)" represents Figure 6.

The gels shown in the figures attached to the declaration do not represent new experimentation; the figures show clearer images of the original gels made at the time that the experiments described in the instant specification were first carried out.

The Examiner asserts that Figure 1 identifies four samples from Alzheimer's patients (ADH-004, ADH-005, ADH-006, ADH-008) wherein ADH-004 and ADH-005 appear not to express Band 4 but ADH-006 and ADH-008 appear to differentially express band 4. The Examiner asserts that this is a contradiction to Applicants' argument because Band 4 is undetectable in Alzheimer's patient samples ADH-004 and ADH-005.

Applicants respectfully disagree with the Examiner's interpretation of Figure 1.

It is evident, in Figure 1 as originally filed and as attached to the declaration, that the band labeled Band 4 is not present in any of the four samples obtained from Alzheimer's patients (ADH-004, ADH-005, ADH-006, ADH-008) but is present in the majority of

samples obtained from patients age matched to the Alzheimer's disease patients (ADC(H)-002, ADC(H)-003, ADC(H)-004). Thus, contrary to the Examiner's assertion, this data does not contradict Applicants' argument since, according to the teachings of the instant invention, SEQ ID NO:3 (obtained from Band 4) is not expressed in Alzheimer's patients.

The Examiner asserts that Figure 3 also identifies four samples from Alzheimer's patients (ADH-004, ADH-005, ADH-006, ADH-008), one pooled normal human serum sample (pooled NHS), and four age matched control samples (ADC(H)-002, ADC(H)-003, ADC(H)-004, ADC(H)-005) wherein Band 4 only appears to be detectable in ADC(H)-002. The Examiner asserts that this is a contradiction to applicants' arguments because Band 4 is not measurable in patients with Alzheimer's disease or is it clearly regulated differently in normal patients.

Applicants respectfully disagree with the Examiner's interpretation of Figure 3.

The data shown in Figure 3 is the same as that in Figure 1 with the exception of the type of chromatography used; Figure 1 was prepared using DEAE 5 elution and Figure 3 was prepared using DEAE 6. Both types of chromatography yielded similar results. Thus, it is evident, in Figure 3 as originally filed and as attached to the declaration, that the band labeled Band 4 is not present in any of

the four samples obtained from Alzheimer's patients (ADH-004, ADH-005, ADH-006, ADH-008) but is present in the majority of samples obtained from patients age matched to the Alzheimer's disease patients (ADC(H)-002, ADC(H)-003, ADC(H)-004). The Examiner asserts that Band 4 is only detectable in ADC(H)-002, however, Applicants' note that Band 4 is clearly pointed out by an arrowhead in ADC(H)-004. Thus, contrary to the Examiner's assertion, this data does not contradict Applicants' argument since, according to the teachings of the instant invention, SEQ ID NO:3 (obtained from Band 4) is not expressed in Alzheimer's patients.

The Examiner asserts that in Figure 6, Band 4 is only seen in patient sample AG-AD-H-004 while all of the other samples do not contain Band 4. The Examiner assert that this is a contradiction to applicants' arguments because Band 4 is not measurable in patients with Alzheimer's disease or is it clearly regulated differently in normal patients.

Applicants respectfully disagree with the Examiner's interpretation of Figure 6.

Figure 6 shows data similar to that shown in Figures 1 and 3. In Figure 6, as originally filed and as attached to the declaration, the band labeled Band 4 is not present in any of the four samples obtained from Alzheimer's patients (AD-H-S-004, AD-H-S-005, AD-H-S-006, AD-H-S-008) but is present in the majority of

samples obtained from patients age matched to the Alzheimer's disease patients (AG-AD-H-S-002, AG-AD-H-S-003, AG-AD-H-S-004). Thus, contrary to the Examiner's assertion, this data does not contradict Applicants' argument since, according to the teachings of the instant invention, SEQ ID NO:3 (obtained from Band 4) is not expressed in Alzheimer's patients.

The Examiner asserts that Applicant contends that the use of SEQ ID NO:3 is well-established because a correlation between the claimed peptide (SEQ ID NO:3) and Alzheimer's disease is evident. This argument appears to be based on immunoglobulin (antibody) light chain proteins involved in amyloidosis and because SEQ ID NO:3 is a fragment of the immunoglobulin kappa light chain. However the Examiner asserts that Stevens merely show an association of kappa light chains in amyloidosis and Lukiw only discuss neuroinflammatory signaling in Alzheimer's disease. No direct link between the immunoglobulin kappa light chain or sequences consisting of SEQ ID NO:3 is taught in either reference.

Applicants respectfully submit that the references (Stevens and Lukiw et al.) were not cited for the purpose of showing a direct link between the immunoglobulin kappa light chain or sequences consisting of SEQ ID NO:3 and Alzheimer's disease. Furthermore, Applicants contend that by requiring the specification to disclose a direct link between the claimed SEQ ID NO:3 and

Alzheimer's disease is requiring the Applicants to meet a standard higher than that which is necessary to satisfy the utility requirement, because it has been settled that an applicant is not required to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt". Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true (MPEP 2164.07 I C).

Applicants respectfully submit that the Stevens and Lukiw et al. references were cited as evidence to show that a person of ordinary skill in the art would be exposed to enough knowledge to conclude that the asserted utility for the claimed biopolymer marker (SEQ ID NO:3) is more likely than not true. Stevens teaches that immunoglobulin light chains are involved in amyloidosis. It is common knowledge that the accumulation of amyloid within the brain is a hallmark of Alzheimer's disease. Lukiw et al. teach that a brain-specific inflammatory response is a major pathogenic mechanism involved in Alzheimer's disease. It is also common knowledge that immunoglobulins can be involved in inflammatory responses.

At page 46, lines 21-23 of the instant specification as originally filed, the claimed biopolymer marker (SEQ ID NO:3) is identified as a fragment of immunoglobulin kappa light chain. When

one of ordinary skill in the art observes that the claimed SEQ ID NO:3, i.e. immunoglobulin kappa light chain, is differentially expressed in Alzheimer's disease patients vs. age-matched patients, they would first want to know whether there is any known connections between Alzheimer's disease and immunoglobulin kappa light chains. After reviewing the teachings of Stevens and Lukiw et al. one of ordinary skill in the art would find it reasonable to believe that the claimed SEQ ID NO:3, i.e. immunoglobulin kappa light chain, more likely than not is linked to Alzheimer's disease.

Thus, Applicants respectfully submit that the references, Stevens and Lukiw et al. were cited to show that the instant invention meets the standards for utility.

Furthermore, when considering practical utility ("real-world" utility) relevant evidence is judged as a whole for its persuasiveness in linking observed properties to suggested uses (*Nelson v. Bowler and Crossley* 206 USPQ 881).

The instant specification suggests that the claimed biopolymer marker (SEQ ID NO:3) is useful for diagnostics and/or therapeutics of Alzheimer's disease since it was found to be differentially expressed in Alzheimer's disease versus a normal physiological state (patients were age-matched to the Alzheimer's disease and were "normal" with respect to a diagnosis of Alzheimer's disease). Applicants respectfully assert that the observed differential

expression is enough evidence such that one of ordinary skill in the art would be reasonably certain of the practical utility of the claimed biopolymer marker (SEQ ID NO:3).

Situations similar to the situation in the instant case have occurred in the prior art wherein a marker was recognized to have practical utility based upon differences in expression in a disease state versus a normal physiological state.

For example, Andreasen et al. disclose a study wherein the differences in concentration of β-amyloid (1-42 aa) in cerebrospinal fluid between early- and late-onset Alzheimer's disease was evaluated. Andreasen et al. found that levels of CSF-β-amyloid were decreased in patients with Alzheimer's disease compared with controls and from these findings suggested that CSF-β-amyloid analyses may be of value in the clinical diagnosis of Alzheimer's disease, especially in the early course of the disease, when drug therapy may have the greatest potential of being effective but clinical diagnosis is particularly difficult (see attached abstract of Andreasen et al. Archives of Neurology 56(6):673-680 1999; reference 1).

Since the data of Andreasen et al. was available in the art at the time of the invention, one of skill in the art would be familiar with such practice and thus likely to find that linking the observed differential expression of the claimed biopolymer

marker (SEQ ID NO:3)to the suggested use of diagnostics and/or therapeutics of Alzheimer's disease is plausible.

The Examiner asserts that the prior art teaches that Alzheimer's disease has no known cure, no known cause or mechanism, and cannot be definitely assigned as a differential diagnosis in the absence of post-mortem examination and cites a reference, Patel, (Journal of Geriatric Psychiatry and Neurology 8:81-95 1995) which allegedly supports this view.

Apparently, the Examiner has dismissed the claimed biopolymer marker (SEQ ID NO:3) as "useless" based upon what Patel is deemed to teach.

First, Applicants draw the Examiner's attention to the fact that the claims, as currently presented, are not drawn to treating, curing or diagnosing Alzheimer's disease. However, even if the claims were drawn to such treatment and/or diagnosis, the fact that there is no known cure for a disease cannot serve as the basis for a conclusion that such an invention lacks utility (see MPEP 2107.03 VI).

Furthermore, the Examiner is reminded that the purpose of the patent system is to **promote** the useful arts (emphasis added by Applicants). Applicants respectfully submit that dismissal of an invention as "useless" simply because it has never been done before does not promote or further encourage medical research.

Patel presents an overview of experimental drug therapy of cognitive impairment in Alzheimer's disease as it was in the early 1990's. Patel does not teach that there is no valid means for diagnostics of Alzheimer's disease other than post-mortem examination. Patel states at page 82, at the top of the left column:

"Over the years, many sets of diagnostic criteria for the clinical diagnosis of AD have been developed and refined, with the result that the diagnostic accuracy of AD has increased significantly. Today, the two most widely used clinical diagnostic criteria are those developed by NINCDS-ADRDA Work Group and the DSM III-R Work Group."

Thus, contrary to the Examiner's assertion, in the past ten years, many methods other than biopsy or post-mortem examination for diagnosing AD have been practiced and regarded as valuable; including Applicants' own patent, US 6,451,547 B1 (Jackowski et al.; reference 2) which claims methods for diagnosing Alzheimer's disease by detecting the presence of biochemical markers in bodily fluid.

In conclusion, based upon all of the above arguments and attached declaration (with figures), Applicants respectfully submit

that one of ordinary skill in the art would immediately appreciate why Applicants regard the claimed biopolymer marker (SEQ ID NO:3) as useful.

Accordingly, Applicants assert that the claimed invention has both a specific and a well-established utility and respectfully request that this rejection under 35 USC 101 now be withdrawn.

Rejection under 35 USC 112, first paragraph

Claim 1, as presented on March 31, 2005, remains rejected under 35 USC 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner asserts that the claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the invention.

The Examiner applies the same arguments used to support the rejection of claim 1 under 35 USC 101 to support the instant rejection of claim 1 under 35 USC 112, first paragraph.

Additionally, the Examiner asserts that Applicants' argument was carefully considered but not found persuasive because the specification must teach how to make and use the invention, not teach how to figure out for oneself how to make and use the invention (*In re Gardner* 166 USPQ 138).

The instant specification discloses that SEQ ID NO:3 was identified as linked to Alzheimer's disease by carrying out mass spectrometry. The mass spectral profile of SEQ ID NO:3, shown in Figure 7, is provided as a reference which can be used by those of ordinary skill in the art to identify the presence of SEQ ID NO:3 in unknown samples. Thus, Applicants respectfully submit that the instant specification meets the requirements under 35 USC 112, first paragraph by teaching how to make and use the invention.

The Examiner additionally asserts that the prior art teaches that immunoglobulin kappa light chains can be linked to infectious disease and autoimmune diseases like Sjögren's Syndrome and cites a reference, Downie-Doyle (Genes and Immunity 3(Supplement 1):S63-65 2002; abstract only) to support this assertion. Accordingly, the Examiner concludes that the claimed immunoglobulin kappa light chains and its fragments could possibly be linked to diseases other than Alzheimer's disease and one of skill in the art would require undue experimentation to distinguish between the particular diseases.

Applicants note that the findings of Downie-Doyle et al. indicate that immunoglobulin kappa light chain gene alleles are not associated with primary Sjögren's Syndrome; however, Downie-Doyle et al. is drawn to immunoglobulin kappa light chain genes and thus, is not relevant to the instant invention which is drawn to

immunoglobulin kappa light chain peptides.

Applicants do not disagree that immunoglobulin kappa light chain peptides can be involved in other disease besides Alzheimer's disease, however, this cannot discount the evidence provided in the specification showing that SEQ ID NO:3 (an immunoglobulin kappa light chain peptide) evidences a link to Alzheimer's disease.

The Examiner is reminded that all questions of enablement should be evaluated against the claimed subject matter and the focus of the examination inquiry should be a question of whether everything within the scope of the claims is enabled (see MPEP 2164.08).

Accordingly, an Applicant is not required to enable material which is not claimed. Applicants do not claim any disease other than Alzheimer's disease nor do they claim an ability to distinguish between disease states. Thus, no teachings regarding these issues are necessary in order to proved evidence for enablement of the pending claims.

In conclusion, Applicants claim that the differential expression of SEQ ID NO:3 between Alzheimer's disease patients and patients age-matched to the Alzheimer's disease patients (determined to be normal with regard to Alzheimer's disease) evidences a link between the claimed biopolymer marker (SEQ ID NO:3) and Alzheimer's disease; a statement which is enabled by the instant specification,

as evidenced by the arguments presented herein in both the section under 35 USC 101 and the instant section. Applicants assert that one of ordinary skill in the art when reviewing the instant specification, given the level of knowledge and skill in the art, would recognize the link between the claimed biopolymer (SEQ ID NO:3) and Alzheimer's disease and would further recognize how to use the claimed biopolymer (SEQ ID NO:3) as a marker for Alzheimer's disease. Thus, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

CONCLUSION

In light of the foregoing remarks and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,

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